AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figures 1 - 3. The Replacement Sheets, which includes Figures 1 - 3, replaces the original sheets including Figures 1 - 3.

Attachment: Replacement Sheets

REMARKS

Applicants appreciate the Examiner's review of the Response filed September 25, 2009. Applicants have carefully reviewed the application in light of the Non-Final Office Action mailed December 7, 2009, by the U.S. Patent and Trademark Office. Applicants previously responded with a response dated June 7, 2010 and a Petition for Three Month Extension of Time. This supplemental amendment is being filed to submit the Declaration of Philippe Caisse and an accompanying explanation of the experiments.

The following remarks are respectfully submitted to illustrate that the application is in condition for allowance. Withdrawal of the rejections and allowance of the claims are respectfully requested.

Claims 1 - 5, 7 - 11 and 13 - 27 are pending in this application. Claims 1, 11 and 27 have been amended to clarify the invention. Support for the claim amendments can be founding the claims and specification as-filed. No new matter is added by this amendment. Claims 6 and 12 have been canceled without prejudice.

Drawings

Applicants submit herewith Replacement Sheets translating text on the drawings into English. No new matter has been added by the amendments. Acceptance of the Replacement Sheets and withdrawal of the drawing objections are respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1–5, 7–12, 17–19, and 21-27 are rejected under 35 U.S.C. § 103(a) over Carvais (U.S. Patent No. 4,902,513), hereinafter "Carvais", in view of Autant et al. (U.S. Patent No. 6,022,562), hereinafter "Autant".

In levying an obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing that the prior art reference teaches or suggests all the claim limitations. *See* M.P.E.P. §§ 2142, 2143. Applicants respectfully submit that the Office Action has failed to

present a prima facie showing of obviousness, and that none of the pending claims are unpatentable over any of the cited reference. Accordingly, Applicants assert Claims 1–5, 7–12, 17–19, and 21-27 are patentable over Carvais in view of Autant and request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

Independent claim 1 requires "wherein the *in vitro* release profile of the suspension of microcapsules in an aqueous liquid phase on day ten is similar to the release profile on day zero, as measured using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C".

The combination of Carvais and Autant does not teach at least this limitation of the claim.

Carvais teaches an oral sustained release medicament containing microcapsules of a drug in a suspension. *See, e.g.*, Carvais at Title, Abstract. The drugs may be water soluble or water insoluble. *See, Id.* at Col. 1, ll. 16-25. The examples teach a water vehicle that is saturated with drug and has microcapsules containing the drug. *See, Id.* at Col. 1, ll. 46-49. Applicants concur with the Examiner that the "only detail provided by Carvais about the microparticles in the taught suspension is the presence of drug." Office Action at page 8; *see also*, page 6. The Examiner concludes that "thus these particles must be coated, uncoated, or a collection of both coated and uncoated particles." *Id.* at page 8. Nowhere does Carvais teach a coating composition ensuring that the release profile is not modified after 10 days in an aqueous liquid phase.

Autant teaches microcapsules that consist of particles that are coated with a mixture of at least one film-forming polymer present in the amount of 50 to 90% by dry weight based on the total weight of the coating composition, at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25% by dry weight based on the total weight of the coating composition, at least one plasticizer present in an amount of 2 to 20% by dry weight based on the total weight of the coating composition, and at least one surfactant or lubricant present in an amount of 2 to 20% by dry weight based on the total weight of the coating composition. *See*, Autant at Col. 6, ll. 55 – Col. 7, ll. 32. The particles are between 50 and 1000 microns. *See, Id.* at Col. 7, ll. 33-35).

Autant is distinct from the current invention because Autant does not teach storing the coated microcapsules in a saturated solution. Moreover, Autant does not teach how to obtain aqueous suspension of coated microcapsules with release profile stable over at least ten days.

The Examiner alleges on page 9, line 11+ of the Office Action that "the release profile claimed by the applicant would necessarily be present in the invention of Carvais in view of Autant et al." Applicants respectfully disagree. The claimed suspension of microparticles has stability of the release profile after 10 days. The "invention of Carvais in view of Autant" did not exist and was not conceivable by the person of ordinary skill in the art at the time the present invention was made. The general teaching in the art of pharmaceutical formulation was that such modified-release microparticles would not be stable when suspended in an aqueous medium. Indeed, Applicants note that in the past 8 years, i.e., since the Autant patent was filed, nowhere does the literature exhibit microparticles according to Autant in a suspension for 10 days. It is then to the merit of the present inventors to have found an unexpected feature of the present invention, where a suspension of microcapsules in an aqueous liquid phase, which allows modified release of an oral active principle, has an *in vitro* release profile on day ten similar to the release profile on day zero.

i. The literature illustrates that one of skill in the art would find the invention to have unexpected results

Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness in making a determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). "[U]nexpected results are evidence of unobviousness." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989).

Applicants submit herewith a Declaration of Catherine CASTAN discussing the unexpected results ("CASTAN Declaration"). As indicated in the Declaration of Catherine CASTAN, it was well-known at the time of the invention that oral release forms had stability problems as shown in the excerpt from Banks et al., "Modern pharmaceutics, Volume 121", 4th Edition, Informa Health Care, pp. 396-8 (2002). CASTAN Declaration at ¶12. Note in particular page 397 where it states: "The formulation of oral sustained-release suspensions has resulted in only limited success due to the difficulty in maintaining the stability of sustained release particles when present in liquid system." The next sentence elaborates that the unsuccessful formulation techniques have included coated beads, drug impregnated wax matrix, microencapsulation, and ion exchange resins. *Id.* As such, it was unexpected for the coated

microcapsules of the claimed invention to provide the beneficial stability characteristics as claimed.

Two of the claimed coating components are water soluble: the nitrogen-containing polymer (P2) and the claimed surfactants. As shown in the previous response, the nitrogen-containing polymer polyacrylamide has a solubility in water of 215g/100ml and is described by practitioners as being "infinitely soluble in water", and the nitrogen-containing polymers poly-N-vinyllactam and poly-N-vinylamide are also known to be water soluble.

The claimed surfactants, anionic surfactants and non-ionic surfactants, are water-soluble.

One of skill in the art would logically believe that addition of water soluble components to a microcapsule coating in an aqueous medium would not result in a formulation where the coating permeability remains unchanged and therefore where the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero.

As indicated in the declaration of Catherine CASTAN, with reference to the document EP 0359195 (Santus), a number of difficulties have been and are still encountered when trying to obtain "controlled release liquid preparations apt to maintain for long times the release characteristics of the pharmaceutical substances contained". CASTAN Declaration at ¶12. To try and maintain the stability of the release characteristics over storage time, Santus suggests the use of several layers, alternating purely hydrophobic coatings with purely hydrophilic coatings. In that context, one of skill in the art would never conceive that a *single* coating, where the hydrophilic and hydrophobic constituents are mixed together within a very thin film, would keep its integrity over time when placed in an aqueous medium; rather the skilled artisan would assume that if microparticles coated in that manner were suspended in water, the soluble constituents of the film would dissolve, causing the loss of the controlled-release properties. In addition, the solution according to the present invention is straightforward to implement. Had it been an obvious solution, Santus would not have had recourse to the complicated and lengthy process of EP 0359195 to solve the problem.

For these reasons, the ordinary skilled artisan could not anticipate the results of the invention. As a consequence, those results are non-obvious, contrary to what is alleged on page 13, last three lines of the Office Action dated 12/07/2009.

On page 14, first three lines of the Office Action, the Examiner suggests that the results of the invention should be compared with the closest prior art. Applicants submit that Carvais is the closest prior art since Carvais is concerned with an objective similar to that of the instant invention, i.e. to provide an oral dosage form for sustained release containing microcapsules of a drug in a suspension. Applicants cannot compare their invention with the teaching of Carvais as Carvais does not provide any quantitative formula, nor does he provide any suggestion as to how to avoid the stability problems that have prevented the development of oral dosage form for sustained release suspensions.

ii. The unexpected results span the claimed range of soluble components in the coating

As noted above, the nitrogen-containing polymer (P2) and the surfactant and/or lubricant are water soluble. The nitrogen-containing polymer (P2) represents 2-25% of the coating, and the surfactant and/or lubricant represent 2-20% of the coating. Applicants assert that it is unexpected that a coating formed of 4-45% water soluble components would maintain its integrity for 10 days in solution.

The inventors have shown that inclusion of two water soluble coating components in the specific claimed coating composition unexpectedly yields a coating that maintains its permeability constant when placed in an aqueous phase for ten days. When calculating the ratio of water soluble compounds in the coating over the total mass of the coating, one finds, in the Examples of the specification as filed, the following values: 17.6 % (Example 1), 18.2 % (Example 3) and 50 % (Example 2). Therefore, the specification as-filed illustrates that the claimed coating maintains its integrity up to 50%.

Applicants further submit herewith a Declaration of Philippe CAISSE, describing additional examples of the invention ("CAISSE Declaration") illustrating that the claimed coating also maintains its integrity when the coating has a ratio of soluble compounds between 10 and 20 %. CAISSE Declaration at ¶¶10-11.

The CAISSE Declaration shows that such coatings still maintained their permeability upon storage in suspension over several days. Therefore the invention is further supported on the extent claimed. From the Examples of the specification and the additional examples disclosed in the Declaration of Philippe CAISSE, it can be seen that one can manufacture the suspensions by adding the sustained-release coated microparticles either into a liquid phase

already saturated by the active principle (specification Ex. 3), or into a liquid phase not saturated by the active principle (specification Ex. 1 & 2 - Declaration Ex. 1 & 2); in the latter case, the liquid rapidly becomes saturated. Therefore in all suspensions the liquid phase is inevitably saturated by the active principle.

In the same Examples the composition of the liquid phase varies to a large extent from only water (Example 2 of the Declaration) to a polymer solution (xanthan gum) (specification Ex. 3 & CAISSE Declaration Ex. 1) or phosphate buffered saline (spec. Ex. 1 & 2). In all cases, with various active principles and irrespective of the composition of the liquid phase, the coating of the microparticles keeps its permeability for at least 10 days. Thus, it shows that the components of the liquid phase do not participate in the unexpected stability of the release profile.

In the claimed invention, the purpose of the coating is to assure a modified release of the active principle. *See*, Abstract. As the claims require, the coated microcapsules stored in an aqueous phase have to have a release profile after ten days that is substantially similar to the release profile at day 0. To maintain this modified release after ten days, the coating must still maintain its permeability. This finding is not obvious in light of the knowledge in the field. In addition, none of the references cited by the Examiner would lead one of skill in the art to believe otherwise.

iii. Other non-claimed coatings do not exhibit the same unexpected results

By this Supplemental Amendment, Applicants further submit a Declaration of Philippe CAISSE, describing additional examples of the invention ("Supplemental CAISSE Declaration"). Supplemental CAISSE Declaration at ¶¶11-13. The Supplemental CAISSE Declaration examined two compositions, each with a coating that falls outside the scope of the instant claims. As discussed below, coatings outside the claimed scope fail to maintain their coating permeability when stored in an aqueous medium for 7 or more days.

Composition 1 was Nuroflex ® LP, which is coated ibuprofen microparticles that provide sustained release of ibuprofen. *Id.* at ¶9. Composition 1 was placed in suspension. The release kinetics of Composition 1 was compared on day 1 with Composition 1 placed in suspension and stored for 9 days. *Id.* at ¶12d. As noted in Figure 1, Composition 1 failed to maintain its release profile after 9 days of storage. *Id.* at Figure 1. Further, saturating the

suspension with ibuprofen did not alter this effect. For instance, Figure 2 compares the release kinetics of Composition 1 placed in a suspension saturated with ibuprofen on day 1 with Composition 1 placed in the saturated suspension for 7 days. *Id.* at ¶12e, Figure 2. Again, release profile curves for Composition 1 were not similar, showing the lack of stability of the release kinetics. *Id.* at ¶12e, Figure 2. Therefore, the sustained release coating of Composition 1 did not keep a constant permeability upon storage in a liquid suspension, and saturating the liquid suspension with the active principle did not alter this effect.

Composition 2 was formed of coated carvedilol phosphate. *Id.* at ¶10. Composition 2 was placed in suspension and the release kinetics was compared on day 1 with Composition 2 stored for 7 days. *Id.* at ¶13e. As noted in Figure 3, Composition 2 failed to maintain its release profile after 7 days of storage, resulting in two very different curves and demonstrating the instability of the particle release kinetics inside the liquid suspension. *Id.* at Figure 3. Further, Figure 4 compares the release kinetics of Composition 2 placed in a suspension saturated with carvedilol phosphate on day 1 with Composition 2 placed in the saturated suspension for 7 days. *Id.* at ¶13f, Figure 4. Again, release profile curves for Composition 2 were different, showing evolution of particle release kinetics in the liquid medium. *Id.* at ¶13f, Figure 4. Therefore, the sustained release coating of Composition 2 did not keep a constant permeability upon storage in a liquid suspension, and saturating the liquid suspension with the active principle did not alter this effect.

Thus, unlike the claimed coating, the coatings of Composition 1 and 2 did not maintain their permeability upon storage in aqueous solution. Further, saturating the aqueous solution with the active principle contained in each Composition failed to maintain the Composition coating permeability, resulting in altered release kinetics.

In contrast, the claimed coating maintains its permeability when stored in an aqueous solution. This finding is not obvious in light of the knowledge in the field. For these reasons, Applicants assert that the invention as claimed is non-obvious over the references, and request the rejection be withdrawn.

Therefore, independent claim 1 is patentable over the cited references. Dependent claims 2–5, 7–12, 17–19, and 21-27 depend from independent claim 1 and add further patentable

features to the patentable features of the independent claims. Withdrawal of the rejection and allowance of the claims are respectfully requested.

Claims 1-2 and 13-16 are rejected under 35 U.S.C. § 103(a) over Carvais in view of Autant and further in view of Türck et al. (U.S. Patent No. 6,184,220), hereinafter "Türck".

Independent claim 1 is patentable over Carvais in view of Autant as described above. The addition of the Türck reference does not remedy the deficiencies of the combination of cited references.

Türck teaches oral suspensions of pharmaceutical substances that contain small amounts of highly dispersed silicon dioxide and hydrophilic polymers to form a three-dimensional siloid structure. *See*, Türck at Title, Abstract. The silicon dioxide and hydrophilic polymers allow the suspension to remain homogeneous, a problem Türck's invention attempts to solve. *See, Id.* at Col. 2, ll. 36-39; Col. 2, l. 65 – Col. 3, l. 2.

Türck is distinct from the current invention because Türck does not teach the required coating of the microcapsules such that the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero. Türck also does not teach microparticles suspended in an aqueous phase that is saturated with the drug.

As such, the combination of the cited references does not render the claimed invention obvious. Therefore, independent claim 1 is patentable over Carvais in view of Autant and further in view of Türck.

Dependent claims 2 and 13-16 depend from independent claim 1 and add further patentable features to the patentable features of the independent claim. Therefore, claims 1-2 and 13-16 are patentable over the cited references. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Claims 1 and 20 are rejected under 35 U.S.C. § 103(a) over Carvais in view of Autant and further in view of Ulrich et al. (U.S. Patent Publication No. 2002/0197327), hereinafter "Ulrich".

Independent claim 1 is patentable over Carvais in view of Autant as described above. The addition of the Ulrich reference does not remedy the deficiencies of the combination of cited references.

Ulrich teaches a taste masking composition of capsules with a drug core and a coating formed of water-insoluble enteric coating. *See*, Ulrich at Title, Abstract. The dried microcapsules can be reconstituted with a liquid vehicle by the pharmacist prior to dispensing. *See, Id.* at [0034].

Ulrich is distinct from the current invention because Ulrich does not teach the required coating of the microcapsules such that the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero. Ulrich also does not teach microparticles suspended in an aqueous saturated solution of the drug. Ulrich also does not teach storing the microcapsules in a saturated solution.

As such, the combination of the cited references does not render the claimed invention obvious. Therefore, independent claim 1 is patentable over Carvais in view of Autant and further in view of Ulrich.

Dependent claims 2 and 13-16 depend from independent claim 1 and add further patentable features to the patentable features of the independent claim. Therefore, claims 1-2 and 13-16 are patentable over the cited references. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Double Patenting Rejections

The Office Action also provisionally rejects various claims for nonstatutory obviousness-type double patenting over various applications by themselves or in view of Carvais. Applicants note that each rejection is provisional by procedure, and also notes that the applications used in the provisional rejections are pending.

The analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887 (Fed. Cir. 1985). The determination of obviousness is a legal conclusion based on underlying factual considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). These factual inquiries include:

1. the scope and content of the prior art;
2. the differences between the prior art and claims at issue;
3. the level of ordinary skill in the pertinent art; and
4. objective evidence of nonobviousness (*i.e.*, secondary considerations).

Graham, 383 U.S. at 17; *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The "determination of obviousness 'does not require absolute predictability of success . . . . [A]ll that is required is a reasonable expectation of success.'" *Brown & Williamson Tobacco Corp.*, 229 F.3d at 1125 (*quoting*, *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)).

In levying an obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing that the prior art references teach or suggests all the claim limitations. *See* M.P.E.P. §§ 2142, 2143. The Supreme Court has also pointed out the "import[ance of] identify[ing] a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (U.S. 2007). Here, the Examiner has not met the burden of demonstrating that the pending claims are obvious.

Nonstatutory obvious-type double patenting rejection over U.S. Ser. No. 10/522,252 in view of Carvais

The Office Action has rejected claims 17-19 and 24-26 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-17 and 19-31 of copending Application No. 10/522,252 ("the '252 application") in view of Carvais. While double patenting rejection may be made in copending applications, in this situation, there would be no need for a terminal disclaimer because the term of the present application will expire before the term of the copending application.

First, Applicants note the priority date of '252 application is July 26, 2002, three months *after* the priority date of this instant application. For this reason alone, the rejection is in err and should be withdrawn. Even despite the priority date, the claims still would not be obvious over the '252 application in view of Carvais. As noted above, the combination of a coating containing two water soluble components with a saturated solution for long term storage, where the drug modified release is the same after ten days, is unexpected and surprising. One of skill in the art would logically understand that a coating formed of water soluble polymers would not maintain its permeability in solution. The Examiner has not shown how the '252 application runs counter to this knowledge. For this reason, Applicants request the rejection be withdrawn.

Nonstatutory obvious-type double patenting rejection over U.S. Ser. No. 11/707,034 in view of Carvais

Claims 1-3, 5, 7-10, 17, 19 and 24-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-9, 11-24, 26, 31, 41-50, 58-76, 89-91, 99-101 and 113 of copending Application No. 11/707,034 ("the '034 application") in view of Carvais. The priority date of the '034 application is June 15, 2005, three years *after* the priority date of this instant application. For this reason alone, the rejection is in err and should be withdrawn. While double patenting rejection may be made in copending applications, in this situation, there would be no need for a terminal disclaimer because the term of the present application will expire before the term of the copending application.

CONCLUSION

Applicant believes the application is now in condition for allowance. Reconsideration and withdrawal of the rejections are requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned below.

Applicants believe no fee is due at this time. In the event that any additional extension of time is necessary to prevent the abandonment of this patent application, then such extension of time is petitioned. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-2228, from which the undersigned is authorized to draw, under Order No. 022290.0120PTUS.

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Respectfully submitted,

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